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PROCESS VALIDATION IN PHARMACEUTICAL INDUSTRY: A REVIEW

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ABSTRACT

Validation is a tool of quality assurance which provides confirmation of the quality in equipment system, manufacturing processes, software and testing methods. Validation assures the products with predetermined quality characteristics and attributes can be reproduced consistently/reproducibly with in the established limits of the manufacturing process operation at the manufacturing site. Validation is required in order to move a product from development to commercial production. Different dosage form have different validation protocol. This paper presents an introduction, basic concepts involved in process validation, approaches for process validation and general overview on process validation in pharmaceutical industry.

Keywords: Process validation, Pharmaceutical industry, Quality assurance, Approaches.

INTRODUCTION

The concept of validation has expanded through the years to encompass a wide range of activities from analytical methods used for the quality control of the drug substances and drug products to computerized systems for clinical trials. In pharmaceutical organizations, validation is a fundamental segment that supports a company commitment to quality assurance. Validation is a tool of quality assurance which provides confirmation of the quality in equipment system, manufacturing processes, software and testing methods. Validation assures the products with predetermined quality characteristics and attributes can be reproduced consistently/reproducibly with in the established limits of the manufacturing process operation at the manufacturing site. Validation is required in order to move a product from development to commercial production. Validation is also effective in minimizing the cost of the financial expenditure of an organization, as a validated process is more efficient and produces less reworks, rejects and wastage [1, 2].

Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves

a series of activities taking place over the lifecycle of the product and process. Process validation is a term used in the medical device industry to indicate that a process has been subject to such scrutiny that the result of the process (a product, a service or other outcome) can be practically guaranteed. This is vitally important if the predetermined requirements of the product can only be assured by destructive testing.

Process validation establishes the flexibility and strict control in the manufacturing process control in the attainment of desirable attributes in the drug products while preventing undesirable properties [3].

As per the ICH guidelines defines as Process validation: 'Process validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of required quality'[4].

Validation of a process entails demonstrating that, when a process is operated within specified limits, it will consistently produce product complying with predetermined (design and development) requirements. In general, the validation of a process is the mechanism or system used by the manufacturer to plan, obtain data, record data, and interpret data. These activities may be considered to fall into three phases: 1) an initial qualification of the equipment used and provision of necessary services – also know as installation qualification (IQ); 2) a demonstration that the process will produce acceptable results and establishment of limits (worst case) of the process parameters – also known as operational qualification (OQ); and 3) and establishment of long term process stability – also known as performance qualification (PQ).

Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. This principle incorporates the understanding that the following conditions exist:

- Quality, safety, and efficacy are designed or built into the product.
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.

According to Indian GMP (Good Manufacturing Practice), validation study is an essential part of GMP required to be done as per predetermined protocols [5].

The FDA defines process validation as follows: Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics [6].

OBJECTIVES OF PROCESS VALIDATION

1) The manufacturing process, in addition to the individual equipment, must be validated.

2) The goal is to create a robust manufacturing process that consistently produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency.

3) A validation plan for the manufacturing process should be drafted and executed by engineers in order to satisfy guidelines. The validation plan usually involves just a PQ section.

4) Just as equipment validation, major changes after the initial validation will result in the need for subsequent revalidation.

5) In the end, process validation will ensure a robust product that is highly reproducible over time.

BASIC CONCEPT OF PROCESS VALIDATION

- Calibration, verification and maintenance of process equipment.
- Prequalification or revalidation.
- Establishing specifications and performance characteristics.
- Selection of methods, process and equipment to ensure the product meets specifications.
- Qualification or validation of process and equipment.
- Testing the final product, using validated analytical methods, in order to meet specifications.
- Challenging, auditing, monitoring or sampling the recognised critical key steps of the process [3].

NEED OF VALIDATION

1. It would not be feasible to use the equipments without knowing whether it will produce the product we wanted or not.
2. The pharmaceutical industry uses expensive materials, sophisticated facilities & equipments and highly qualified personnel.
3. The efficient use of these resources is necessary for the continued success of the industry. The cost of product failures, rejects, reworks, and recalls, complaints are the significant parts of the total production cost.
4. Detailed study and control of the manufacturing process- validation is necessary if failure to be reduced and productivity improved.
5. The pharmaceutical industries are concerned about validation because of the following reasons.
6. Assurance of quality.
7. Cost reduction.
8. Government regulation [7,8].

STAGES OF PROCESS VALIDATION

The three stages of process validation are;

Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

Stage 1 includes performing process understanding studies to establish all process parameters, determining which parameters are critical, and executing supporting validation studies. Process design is the activity of defining the commercial manufacturing process that will be reflected in planned master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.

Stage 2 includes the performance of three consecutive runs at the intended commercial scale. During the process qualification (PQ) stage of process validation, the process design is evaluated to determine if it is capable of reproducible commercial manufacture.

This stage has two elements: (1) design of the facility and qualification of the equipment and utilities and (2) process performance qualification (PPQ). During Stage 2, CGMP-compliant procedures must be followed. Successful completion of Stage 2 is necessary before commercial distribution. Products manufactured during this stage, if acceptable, can be released for distribution.

STAGE 1: PROCESS PRE – QUALIFICATION	STAGE 2: PROCESS QUALIFICATION	STAGE 3: LIFECYCLE QUALIFICATION
Parameter risk assessment ↓ Range studies ↓ Critical parameter determination	At least 3 consecutive runs at scale	Statistical process control Change control Re-validation

Stage 3 is the ongoing assessment of process performance through life cycle qualification and management of process changes. The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. Adherence to the CGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, will allow detection of undesired process variability [9, 10].

PLANING FOR VALIDATION

All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.

- The VMP should be a summary document, which is brief, concise and clear.
- The VMP should contain data on at least the following:

1. Validation policy.
2. Organisational structure of validation activities.
3. Summary of facilities, systems, equipment and processes to be validated.

4. Documentation format: The format to be used for protocols and reports.

5. Planning and scheduling.

6. Change control.

7. Reference to existing document.

8. Incase of large projects, it may be necessary to create separate validation master plans [11]. **TYPES OF VALIDATION**

Validation can be prospective, concurrent, retrospective or revalidation (repeated validation).

- **Prospective validation:** Prospective validation is defined as the establishment of documented evidence that a system does what it purports to do based on a pre planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process. This approach to validation is normally under taken when ever new formula, process or facility must be validated before routine pharmaceutical formulation commences. In fact validation of process by this approach often leads to transfer of the manufacturing process from the development function to product. The objective of prospective validation is to prove or demonstrate that the process will work in accordance with a validation master plan or protocol prepared for pilot product trails.
- **Retrospective validation**: Retrospective validation is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of historical information. The sources of such data are production, QA and QC records. The issues to be addressed here are changes to equipment, process, specification and other relevant changes in the past.
- **Concurrent validation**: It is similar to the prospective, except the operating firm will sell the product during the qualification runs, to the public as its market price. This validation involves in process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control.
- **Revalidation**: It is the repetition of a validation process or a part of it. This is carried out when there is any change or replacement in formulation, equipment

plan or site location, batch size and in the case of sequential batches that do not meet product specifications and is also carried out at specific time intervals in case of no changes [2, 12, 13].

STRATEGY FOR VALIDATION OF METHODS

The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to the unknown samples analyzed in the routine. The preparation and execution should follow a validation protocol preferably written in a step by step instruction format as follows:

- Develop a validation protocol or operating procedure for the validation.
- Define the application purpose and scope of method.
- Define the performance parameters and acceptance criteria.
- Define validation experiments.
- Verify relevant performance characteristics of the equipment.
- Select quality materials, e.g. standards and reagents;
- Perform pre-validation experiments;
- Adjust method parameters and/or acceptance criteria, if necessary;
- Perform full internal and external validation experiments;
- Develop SOPs, for executing the method routinely;
- Define criteria for revalidation.
- Define type and frequency of system suitability tests and/ or analytical quality control (AQC) checks for the routine; and
- Document validation experiments and results in the validation report [14].

VALIDATION PROTOCOLS

Protocol should specify the following in details;

- General information.
- Objective.
- Background/revalidation.
- Summary of development and technical transfer (form R & D or another site activity to justify in process testing and controls: any previous validations.
- List of equipments and their qualification status.

- Facilities qualification.
- Process flow chart.
- Manufacturing procedure narrative.
- List of critical processing parameters and critical excipients.
- Sampling, test and specification.
- Acceptance criteria.

Validation protocol is a written plan stating how validation will be conducted. The document should give details of critical steps of manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be tested [2].

According to Indian GMP (Good Manufacturing Practice), validation study is an essential part of GMP required to be done as per predetermined protocols. Prospective process validation is carried out during the development stage by means of risk analysis of the production process which is broken down into individual steps. These are then evaluated on the basis of past experience to determine whether they might lead to critical situation The risk is evaluated, the potential causes are investigated and assessed for probability & extent, the teal plan are drawn up, & priorities are set. The trial are then performed and evaluated & overall assessment is made. If the end results are acceptable the process is considered to be satisfactory. Unsatisfactory processes must be modified & improved until a validation exercise proves them to be satisfactory. This form of validation is essential in order to limit the risk of error occurring on the production scale. The present work deals with identification of critical stage and their consequent evaluation by challenging its upper and lower specifications [15].

IMPORTANCE OF PROCESS VALIDATION

The main advantages to be obtained from validation are assurance of quality and process optimization, both resulting in a reduction of total costs.

Assurance of Quality

Validation is an extension of the concepts of quality assurance since close control of the process is necessary to assure product quality and it is not possible to control a process properly without thorough knowledge of the capabilities of that process without validated

and controlled processes, it is impossible to produce quality products consistently. End product testing, in the absence of validation, gives little assurance of quality for variety reasons, among which are

1. Very limited sample size.

2. The limited number of tests performed on a sample. For example, it is impractical to test for all potential impurities or contaminants.

3. The limited sensitivity of the test.

Process Optimization

The optimization of a process for maximum efficiency, while maintaining quality standards, is a

consequence of validation. Literal meaning of word to optimize is "To make as effective, perfect or useful as possible". The optimization of the facility, equipment, systems, and processes results in a product that meets quality requirements at the lowest cost.

Reduction of quality costs

Quality costs are divided in to four categories. They are:

a) Preventive costs.

b) Appraisal costs.

c) Internal failure costs.

d) External failure costs.

e.g. of internal failure costs: Any validated and controlled process will result in fewer internal failures like

Fewer rejects

Reworks

Re-tests

Re-inspection

Process validation makes it possible to do the job right the first time. Also, a scientifically studied and controlled process makes it unlikely that defective products will be dispatched to market thus no recalls or market complaints [15].

APPROACHES TO PROCESS VALIDATION

There are two basic approaches to the validation of the process itself (apart from the qualification of equipment used in production, the calibration of control and measurement

instruments, the evaluation of environmental factors, etc). These are the experimental approach and the approach based on the analysis of historical data. The experimental approach, which is applicable to both prospective and concurrent validation, may involve:

1. extensive product testing,
2. simulation process trials,
3. challenge/worst case trials, and
4. Control of process parameters (mostly physical) [16].

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to the extent greater than that required inroutine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and specifications, and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the normality of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are within compendia specifications [17].

VALIDATION TEAM

A multidisciplinary team is primarily responsible for conducting and supervising validation studies. Personnel qualified by training and experience in a relevant discipline may conduct such studies. The working party would usually include the following staff members such as;

Head of quality assurance.

Head of engineering.

Validation manager.

Production manager.

Specialist validation discipline: all areas [18].

VALIDATION REPORT

A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized (signed and dated). The report should include at least the following:

- Title and objective of study.
- Reference to protocol.
- Details of material.
- Equipment.
- Programmes and cycles used.
- Details of procedures and test methods.
- Results (compared with acceptance criteria).
- Recommendations on the limit and criteria to be applied on future basis [19].

CONCLUSION

Validation is the commonest word in the area of drug development, manufacturing and specification of finished products. Pharmaceutical validation which includes assay validation, cleaning validation, equipment validation as well as the overall process validation is crucial in stability analysis, animal studies and early phases of clinical development such as bioavailability/bioequivalence studies. So it is necessary, before approval of a new drug, that an accurate and reliable assessment for its effectiveness and safety for the intended indication and target patient population is demonstrated.

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